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(54) Title: PROCESS AND NOVEL INTERMEDIATES**(57) Abstract**

This invention provides intermediates and processes useful for the preparation of crytophycin compounds.

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PROCESS AND NOVEL INTERMEDIATES

This invention relates to the fields of pharmaceutical and organic chemistry and provides novel intermediates and processes useful for the preparation of cryptophycin compounds.

Antimetabolites have been used for a number of years as chemotherapeutic agents in the treatment of cancer. A new class of antimetabolites, cryptophycin compounds are useful for disrupting the microtubule system and, thus, can be useful for the treatment of cancer. In order to produce sufficient quantities of these compounds, there is a need for efficient totally synthetic processes for their preparation.

The novel processes and intermediates of this invention are important elements in providing an efficient route for preparing other cryptophycin intermediates. A special advantage provided is that the intermediates thus prepared have only minimal residual impurities. Ultimately, these intermediates can be linked to provide a total synthesis of cryptophycin compounds.

A number of problems must be resolved in order to accomplish a large scale total synthesis of a complex molecule such as the cryptophycin molecule. It is difficult to obtain intervening intermediates of sufficient purity, to be able to handle the materials easily and to obtain reliable yields when processes are carried out on the scale

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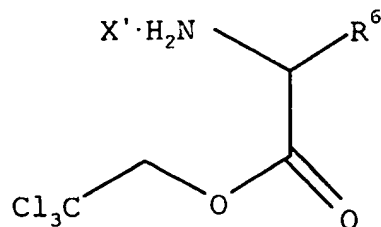
needed to obtain the quantities of compounds needed for pharmaceutical purposes.

The novel intermediates and processes of this invention accomplish some of these goals. For example, one of the processes permits removal of a protecting group to provide an intermediate that can now be isolated as a convenient white solid. The new coupling process results in unexpectedly greater yields and avoids what previously was an extra step of preparing a pentafluorophenyldiphenylphosphinic chloride coupling reagent. A rhodium-catalyzed process prepares a novel fragment, called Fragment C', that is useful for an alternative synthesis of cryptophycin compounds. Another process that is applicable to acid-and base sensitive products minimizes recrystallization and chromatography steps.

Thus, the processes and intermediates of this invention are important advances in the synthesis of useful cryptophycin compounds. These advances include, but are not limited to, increased efficiency, decreased cost, and improved purity.

In one aspect, this invention provides a novel intermediate of Formula XII

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XII

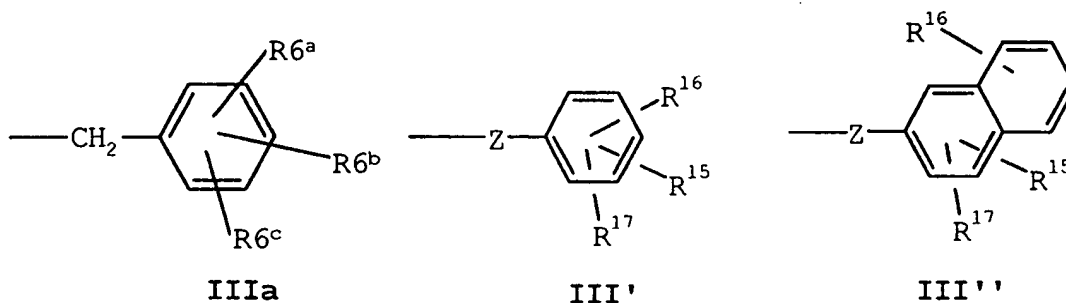
wherein X' represents a strong acid; and

R^6 is C_1 - C_6 alkyl, substituted (C_1 - C_6)alkyl, (C_3 - C_8)cycloalkyl,

5 substituted C_3 - C_8 cycloalkyl, a heteroaromatic or

substituted heteroaromatic group, or a group of formula

IIIa, III' or III'':



10

wherein

R^{6a} , R^{6b} , and R^{6c} independently are H, halo or OR^{18} ;

R^{15} , R^{16} , and R^{17} independently are hydrogen, halo, (C_1 - C_6)alkyl, OR^{18} , O-aryl, NH_2 , $\text{NR}^{18}\text{R}^{19}$, NO_2 , $\text{OP}(\text{O})_2\text{H}_2$, (C_1 - C_6

15 alkoxy)phenyl, Sbenzyl, CONH_2 , CO_2H , PO_3H_2 , SO_2R^{23} , or Z' ;

R^{18} and R^{19} independently are hydrogen or C_1 - C_6 alkyl;

R^{23} is hydrogen or (C_1 - C_3)alkyl;

Z is $-(\text{CH}_2)_n-$ or (C_3 - C_5)cycloalkyl;

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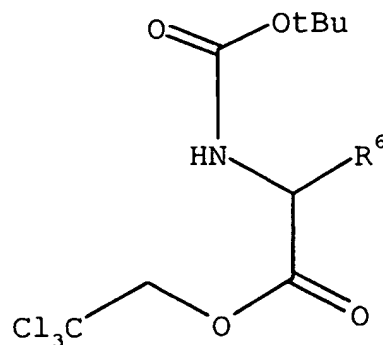
n is 0, 1, or 2; and

Z' is an aromatic or substituted aromatic group.

Further, this invention provides a process for preparing an intermediate of Formula XII as defined supra,

5 comprising

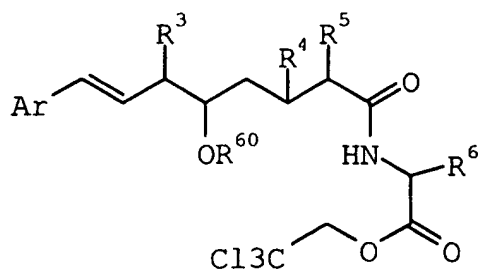
contacting a compound of the formula XII'



XII'

with a strong acid.

10 In another aspect, this invention provides a new coupling process for preparing compounds of Formula XIII (known as Fragment A-B of the cryptophycins):



XIII

15 wherein

Ar is an aromatic or heteroaromatic group, or a substituted aromatic or heteroaromatic group;

R^{60} is an alcohol protecting group;

R^3 is C_1-C_6 alkyl;

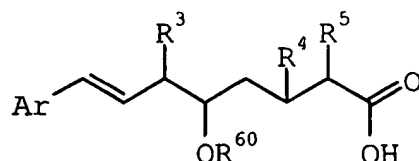
R^4 and R^5 are H; or

R^4 and R^5 together form a second bond;

5 R^6 is as defined supra;

comprising contacting a compound of Formula XII as defined supra,

with 1) a compound of Formula XV



XV

10 wherein Ar, R^3 , R^4 , R^5 and R^{60} are as defined supra;

2) an $(R^A)_2$ phosphinic halide, wherein R^A is C_1-C_6 alkyl, C_1-C_6 aralkyl, or Ar; and 3) a base.

Furthermore, this invention provides an improved
15 process for preparing a compound of Formula XIII, as defined supra,

comprising

reacting a compound of Formula XII, as defined supra, with a compound of formula XV as defined supra, in the presence of

20 1) the coupling reagent diphenyl chlorophosphate $[(PhO)_2P(O)Cl]$; and 2) an amine.

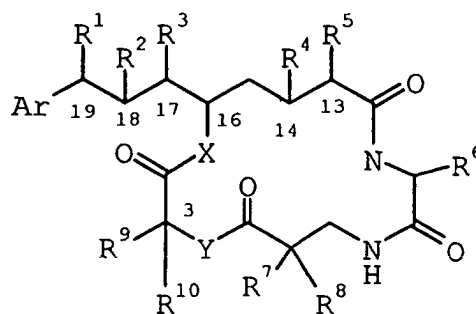
Carboxyl activation via phosphorous based reagents is an often used method for the synthesis of amides and related

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compounds. The particular method employed by Barrow *et al.* (J. Am. Chem. Soc. 1995, 117, 2479-2490) for the synthesis of the formula XIII compound wherein Ar=Ph, R³=Me, R⁶⁰=TBS, R⁴ and R⁵=a second bond; and R⁶=3-chloro-4-methoxybenzyl

5 (compound 4 *infra*) utilized pentafluorophenyl diphenylphosphinic chloride (FDPP) as the coupling reagent. That reaction only afforded compound 4 in 65% yield after silica gel chromatography. Thus, that method suffered from low yield (65%) and required FDPP preparation because it is
 10 not commercially available. The improved coupling procedure of this invention is advantageous in that it does not require preparation of the reagent [(PhO)₂P(O)Cl], and it gives higher yields (78%). Additionally, using (PhO)₂P(O)Cl provides a significant cost advantage.

15 In yet another aspect, this invention provides a process for preparing a compound of Formula I



I

wherein

20 Ar, R³, R⁴, R⁵ and R⁶ are as defined supra;

R¹ is halo, SR, OR, amino, mono or di-(C₁-C₆-alkyl)amino,

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tri(C₁-C₆-alkyl)ammonium, C₁-C₆-alkylthio, di(C₁-C₆-alkyl)sulfonium, C₁-C₆-alkylsulfonyl, or C₁-C₆-alkylphosphonyl; and

R² is OH or SH; or

5 R¹ and R² taken together form a second bond between C-18 and C-19 or together form an epoxide, aziridine, episulfide, or cyclopropyl ring;

R is H, C₁-C₆ alkyl, C₁-C₆ alkanoyl or Ar;

R⁷ is H, C₁-C₆ alkyl, C₂-C₆-alkenyl, C₂-C₆-alkynyl, benzyl, or

10 benzyl substituted with up to three substituents

independently selected from C₁-C₆-alkyl, halo, C₁-C₆-alkoxy, amino or NR⁵¹R⁵²; and

R⁸ is H or C₁-C₆ alkyl; or

R⁷ and R⁸ together form a C₃-C₈ cycloalkyl ring;

15 R⁵¹ and R⁵² independently are C₁-C₃ alkyl;

R⁹ is H, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆-alkynyl or (C₁-C₆ alkyl)C₃-C₅ cycloalkyl;

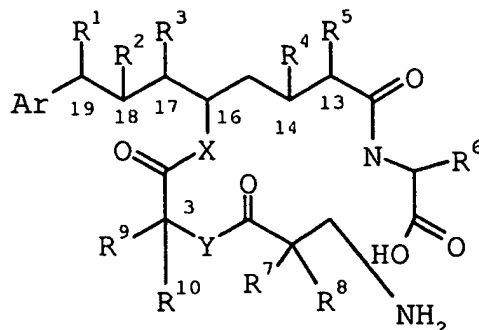
R¹⁰ is H or C₁-C₆ alkyl;

X is O, NH or (C₁-C₃ alkyl)N-; and

20 Y is C, O, NH, S, SO, SO₂ or (C₁-C₃ alkyl)N-;

comprising

contacting 1) a compound of Formula XVI

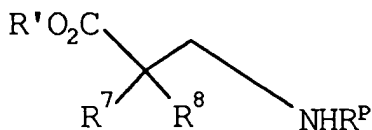


XVI

wherein Ar, X, Y, R¹, R², R³, R⁴, R⁵, R⁶, R⁷, R⁸, R⁹, and R¹⁰
are as defined supra;

- 5 with 2) an $(R^A)_2$ phosphinic halide,
wherein R^A is as defined supra; and
3) a base.

This invention also provides a process for preparing a compound of Formula **XVII**

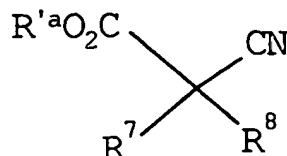


XVII

wherein R' is hydrogen or C₁-C₆ alkyl;
R⁷ and R⁸ are as defined supra; and
R^p is *tert*-butoxycarbonyl or benzyloxycarbonyl;

- 15 **comprising**
- contacting a compound of Formula XVIII

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**XVIII**

wherein R'^a is C₁-C₆ alkyl,

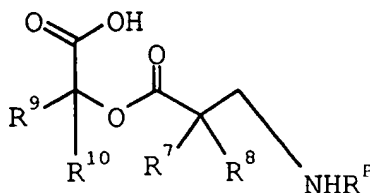
with a rhodium catalyst and hydrogen gas; and optionally

5 hydrolyzing the product to obtain the compound wherein R' is hydrogen.

Processes where R⁷=R⁸ are preferred embodiments of this invention.

In another aspect, this invention provides a

10 process for preparing a compound of Formula **XIX**

**XIX**

wherein

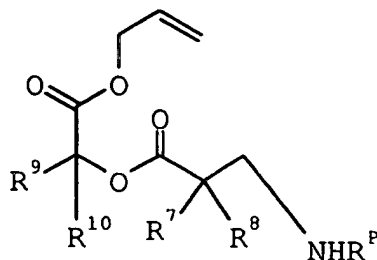
R⁷, R⁸, R⁹ and R¹⁰ independently are H or C₁-C₆ alkyl;

15 R^p is *tert*-butoxycarbonyl (BOC) or benzyloxycarbonyl;

comprising

contacting a compound of Formula **XX**

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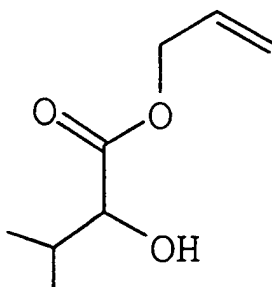
**XX**

in the presence of

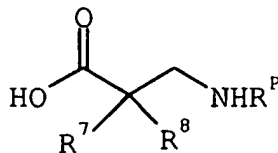
1) a catalytic quantity of $\text{Pd}(\text{PPh}_3)_4$, wherein the
 5 catalytic quantity is less than about four (4) mole percent,
 and

2) an allyl scavenger.

In addition, this invention provides an
 improvement in the process for preparing a compound of
 10 formula **XX** by coupling a Fragment D compound of the formula:

**D**

and a Fragment C compound of the formula:

**C**

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wherein R^7 and R^8 are as defined supra, but provided R^7 and R^8 cannot be H, in an inert organic solvent;

the improvement comprising using the coupling reagent 1,1'-carbonyldiimidazole (CDI). This process provides a

5 significant improvement in yields of Fragment C compound.

In addition, costs are reduced, and it is easier to remove unwanted by-products.

The phrase "catalytic quantity" refers to less than a stoichiometric amount, but an amount sufficient to
10 achieve the desired results. The term is intended to have the meaning commonly understood in the art.

The term "alkyl" refers to an alkyl group with the designated number of carbon atoms. It may be saturated or unsaturated, and branched or straight chain. "Lower alkyl"
15 means a C_1 - C_5 alkyl group. Examples of such alkyl groups include methyl, ethyl, n-propyl, isopropyl, n-butyl, propenyl, sec-butyl, n-pentyl, isobutyl, tert-butyl, sec-butyl, methyl-substituted butyl groups, pentyl, tert-pentyl, sec-pentyl, methyl-substituted pentyl groups and the like.

20 "Substituted alkyl" refers to a C_1 - C_6 alkyl group that may include up to three (3) substituents containing one or more heteroatoms. Examples of such substituents are OH, NH_2 , $CONH_2$, CO_2H , PO_3H_2 and SO_2R^{21} wherein R^{21} is hydrogen, C_1 - C_3 alkyl or aryl.

25 The term "cycloalkyl" refers to a saturated C_3 - C_8 cycloalkyl group. A "substituted cycloalkyl group" refers

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to a cycloalkyl group having up to three C₁-C₃ alkyl, halo, or OR²¹ substituents. The substituents may be attached at any available carbon atom. Cyclohexyl is an especially preferred cycloalkyl group.

5 "Lower alkoxy" means a C₁-C₅ alkyl group bonded to an oxygen atom.

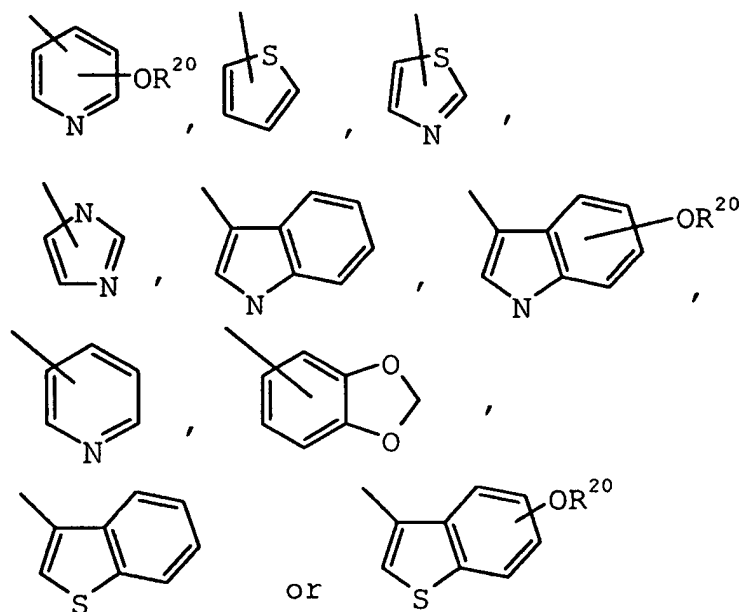
 The term "allyl" means a 2-propenyl group. The term "allyl scavenger" is commonly understood in the art. Preferred allyl scavengers are pyrrolidine, piperidine,
10 morpholine, and 1,3-dicarbonyl compounds. An especially preferred allyl scavenger is morpholine.

 The term "halo" refers to Cl, Br, F, or I.

 The terms "aromatic group" and "heteroaromatic group" refer to common aromatic rings having 4n + 2 pi
15 electrons in a monocyclic or bicyclic conjugated system. The term "aryl" refers to an aromatic group, and the term "aralkyl" refers to an aryl(C₁-C₆-alkyl) group. Examples of aromatic groups are phenyl, benzyl and naphthyl.

Heteroaromatic groups will contain one or more oxygen,
20 nitrogen and/or sulfur atoms in the ring. Examples of heteroaromatic groups include furyl, pyrrolyl, thienyl, pyridyl and the like. When the aromatic or heteroaromatic groups are substituted, they may have from one to three independently selected C₁-C₇ alkyl, C₁-C₆-alkoxy or halo
25 substituents. The substituents may be attached at any available carbon atom.

Especially preferred heterocyclic groups are



wherein R^{20} is hydrogen or C_1 - C_6 alkyl.

5 The term "amino protecting group" refers to a standard amino protecting group that is either acid labile or can be removed under mildly basic to neutral conditions. Such groups are well known in the art. [See, for example, J.F.W. McOmie, "Protective Groups in Organic Chemistry",
10 Plenum Press, (London and New York, 1973); Greene, T.W. "Protecting Groups in Organic Synthesis", Wiley (New York, 1981)]. Preferred amino protecting groups are acid labile. An especially preferred amino protecting group for compounds of Formula XVII is tert-butoxycarbonyl ("BOC"). When the R^6
15 substituent in a Formula I compound contains an amino substituent, it must be protected using an amino protecting group.

The term "alcohol protecting group" is one that is introduced during a portion of the synthetic process to protect an alcohol group that might otherwise react in the course of chemical manipulations. The group is then removed
5 at a later stage of the synthesis. Reactions for the formation and removal of such protecting groups are described in a number of standard works, including the two references listed supra. A particularly useful alcohol protecting group is tert-butyldimethylsilyl (TBS).

10 The processes of this invention are preferably carried out in the presence of a solvent. Selection of an appropriate solvent is commonly understood in the art. An inert organic solvent, such as N,N-dimethylformamide (DMF), ethyl acetate, dichloromethane, toluene or acetonitrile, or
15 a mixture thereof, is recommended.

"Epoxide ring" means a three-membered ring whose backbone consists of two carbon and one oxygen atoms.

"Aziridine ring" means a three-membered ring whose backbone consists of two carbon and one nitrogen atoms. "Episulfide
20 ring" refers to a three-membered ring whose backbone consists of two carbon and one sulfur atoms.

Examples of methods of halogenation include the addition of hydrogen halides, free radical halogenation, etc. Such methods are known in the art.

25 The term "strong acid" refers to an acid that has a pKa of 2 or less. A hydrohalic acid is most suitable. A

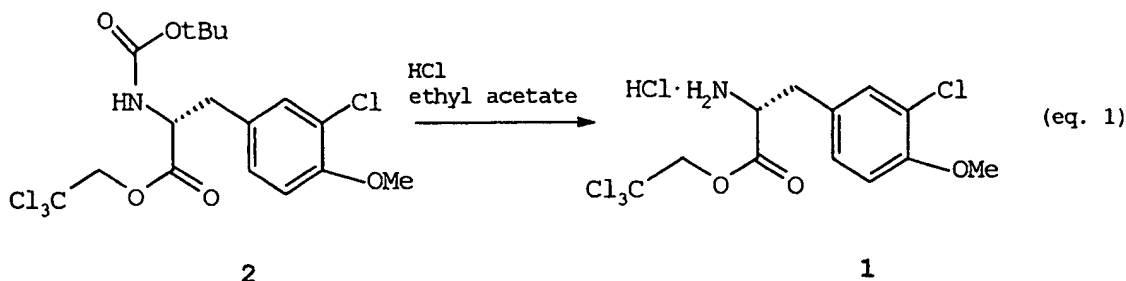
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preferred hydrohalic acid is hydrochloric acid. Other mineral acids, such as phosphoric and sulfuric, and organic acids, such as tosic and acetic, may also be used.

The term "base" has its accepted meaning. Thus, a base is a compound that yields hydroxyl ions in water or the negative ion of a solvent; or a base is any molecule or ion that can combine with protons or hydrogen ions, i.e. a proton acceptor. The term includes, but is not limited to, N,N-diisopropylethylamine, carbonates, and other tertiary amines.

Many of the cryptophycin compounds prepared by the processes of this invention are known. As used herein, the term refers to both known cryptophycins and to new cryptophycin compounds of Formula I, as defined supra.

The process for preparing a formula XII compound that is a hydrochloride salt is illustrated by equation 1:

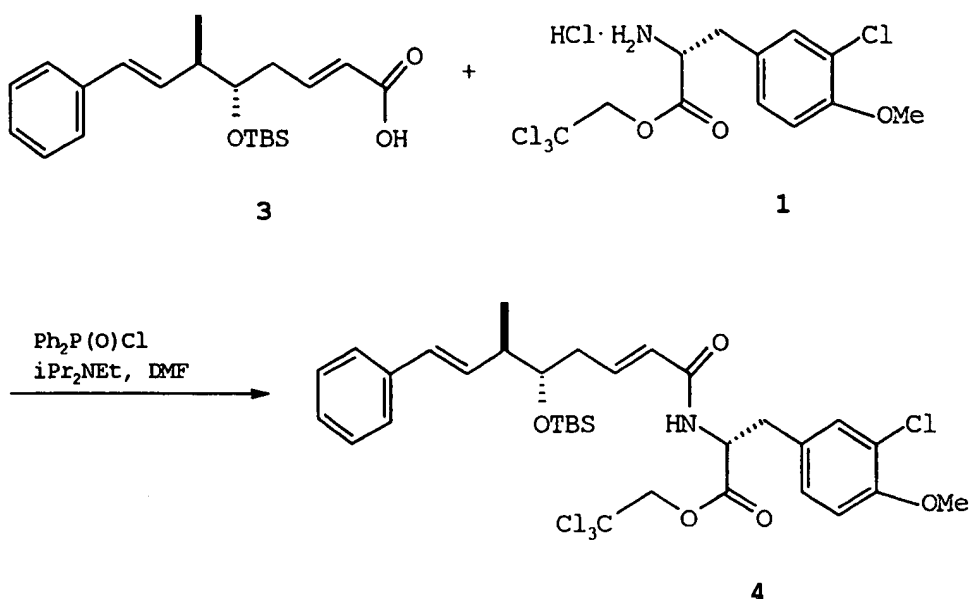


Other R⁶ groups can be substituted for the chloromethoxybenzyl group.

The first process for preparing the enamide fragment 4 is illustrated in equation 2.

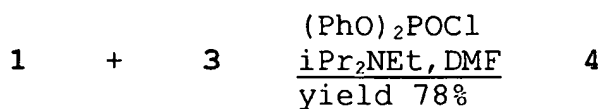
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(eq. 2)



In Eq. 2, TBS refers to a tert-butyldimethylsilyl group.

The improved process of preparing Fragment 4 is illustrated in Equation 3.



(eq. 3)

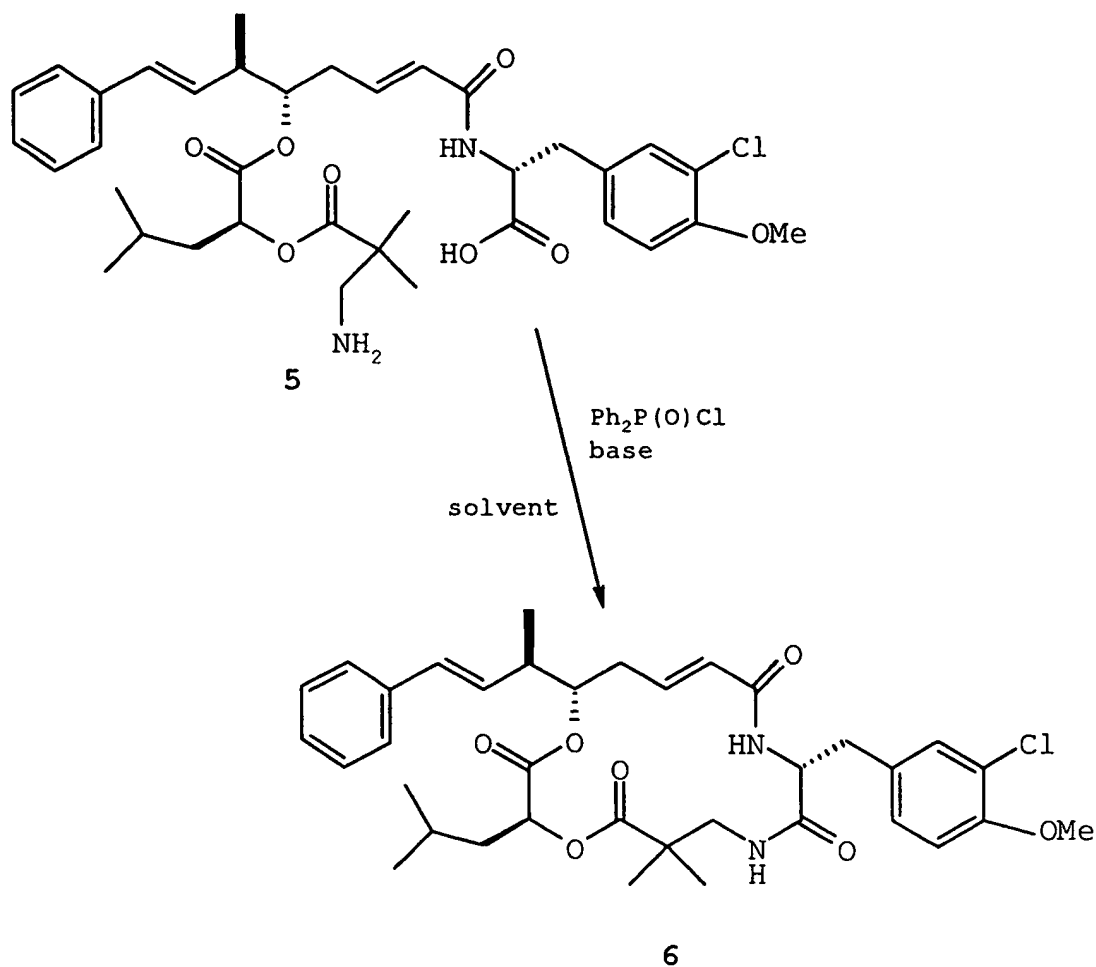
Equations 2 and 3 are applicable to corresponding intermediates having various Ar, R⁶⁰, and R⁶ groups.

Although DMF and N,N-diisopropylethylamine are the illustrated solvent-base used in equations 2 and 3, and in that of equation 4 infra, any nonparticipating solvent or solvent combination-base will be appropriate for the processes. Typical solvents include ethers, halogenated hydrocarbons, and esters. Typical bases include tertiary

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amines and carbonates. An especially preferred base for these processes is diisopropylethylamine.

The process for preparing an illustrative macrolactam of Formula I is illustrated by equation 4:

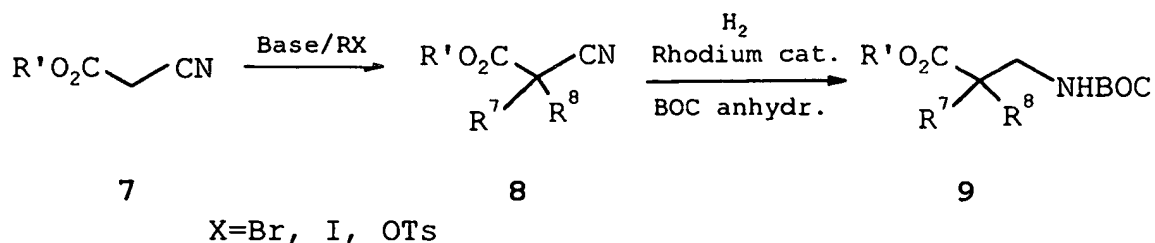


(eq. 4)

An especially preferred solvent for the process of eq. 4 is DMF. This process is especially useful because it provides improved yields. In addition, it makes it possible to use $\text{Ph}_2\text{P}(\text{O})\text{Cl}$, which is commercially available, to complete the macrolactamization.

The process for preparing a compound of Formula

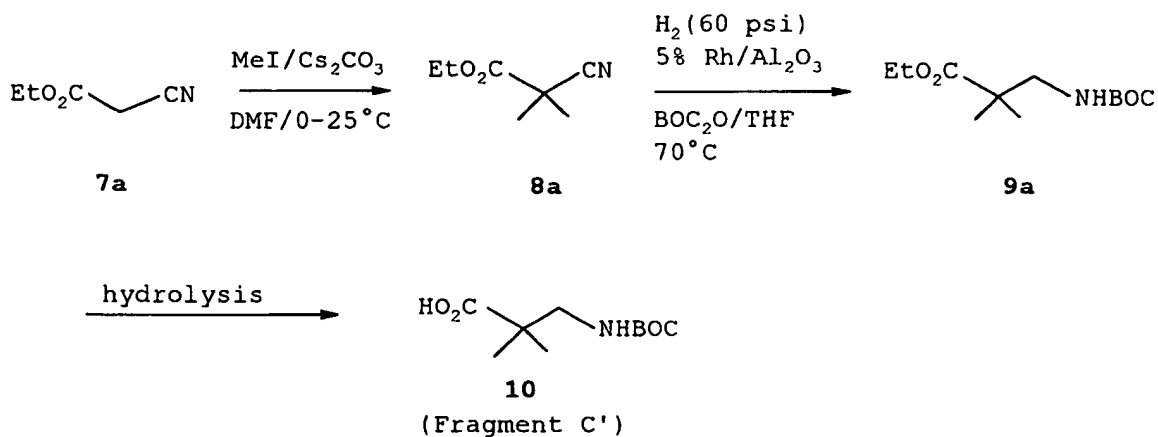
XVII wherein R^P=BOC is illustrated by Equation 5.



(eq. 5)

5 This process is especially useful because it is amenable to scale up, is cost effective, and provides good product yields.

Preparation of a specific compound of Formula XVII is illustrated by Equation 6.



(eq. 6)

Compound **8a** is a known compound. It has been prepared by the reaction of ethyl cyanoacetate with methyl iodide in the presence of sodium ethoxide,^{a,b} and sodium hydride.^c [a)

15 Hessler, J.C. *J. Am. Chem. Soc.* 1913, **35**, 990. b)

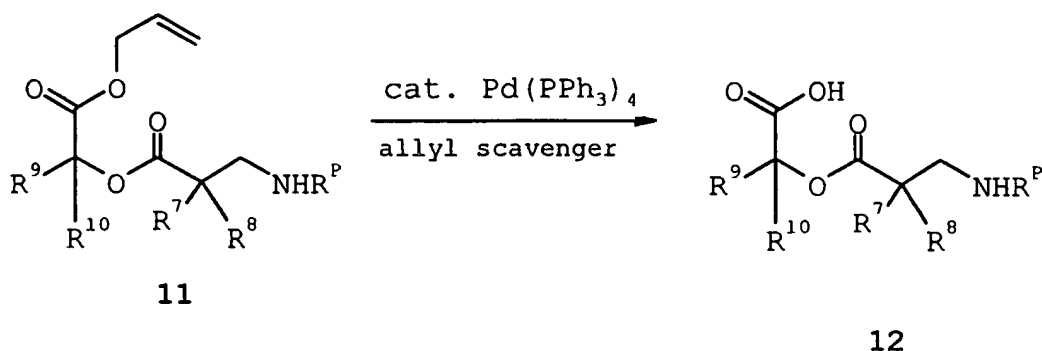
Biechler, S.S. and Taft, R.W. *J. Am. Chem. Soc.* 1957, **79**,

4928. c) Thompson, H. W. and Swistok, J. *J. Org. Chem.*
1981, 46, 4907].

Appropriate hydrolysis conditions for preparing
Compound 10 from Compound 9a can be readily determined.

5 Especially preferred hydrolysis agents are LiOH and NaOH.

The new allyl ester deprotection process is
illustrated by Equation 7:



(eq. 7)

In the compounds in Equation 7, R^p , R^7 , R^8 , R^9 and R^{10} have the meanings defined supra.

As illustrated, the $\text{Pd(PPh}_3)_4$ catalyst should be
present in an amount less than about four (4) mole percent.

15 Preferably, the amount of $\text{Pd(PPh}_3)_4$ catalyst is less than
two mole percent (2 %). It is especially preferred that the
amount of $\text{Pd(PPh}_3)_4$ catalyst is about two tenths mole percent
(0.2%) or less. In addition, using less catalyst provides a
significant cost advantage.

20 A preferred embodiment of the Equation 7 process
is when R^9 is isobutyl, and R^{10} is hydrogen. Especially

preferred are compounds 11 and 12 wherein $R^P=BOC$, $R^9=iBu$, $R^{10}=H$, and R^7 and $R^8=Me$ (compounds 11a and 12a) or R^7 and $R^8=H$ (compounds 11b and 12b).

An especially preferred allyl scavenger is
5 morpholine.

Preferred solvents for the process of Equation 7 are tetrahydrofuran, acetone, alcohols, acetonitrile, and ethyl acetate. An especially preferred solvent is tetrahydrofuran.

10 The use of the allyl ester as a protecting group for carboxylic acids is well known and has been the subject of reviews. Kocienski, P. J. *Protecting Groups*; Georg Thieme Verlag: Stuttgart, 1994; pp 139-154; Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, 2nd
15 Edition; John Wiley and Sons, Inc.: New York, 1991; pp 248-9; and Tsuji, J.; Minami, I. *Acc. Chem. Res.* 1987, 20, 140-45. The allyl ester deprotection process in the literature uses ten (10) mole percent $Pd(PPh_3)_4$. Barrow, R. A.; Hemscheidt, T.; Liang, J.; Paik, S.; Moore, R. E.;
20 Tius, M. A. *J. Am. Chem. Soc.* 1995, 117, 2479.

In the case of complex substrates such as 12 that are sensitive to the acidic and/or basic conditions used in subsequent isolation steps, isolation of pure product is problematic. The protecting group in 12 is generally not
25 stable below pH 2-3, and the ester group of 12 can be

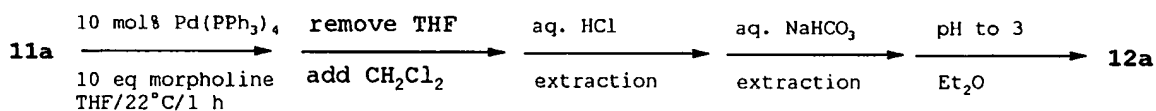
-21-

cleaved by base (hydroxide). Isolation and purification were even more significant issues for 12, because it could not be purified easily. Thus, there was a need to streamline the work-up and avoid exposure of 12 to aqueous acids or bases.

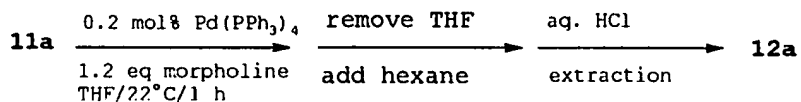
The present process provides surprisingly greater yields, fewer undesired impurities in the product, and allows isolation of acid-sensitive products without crystallization or chromatography of the product.

Procedures A and B illustrate the isolation advantage of the new process over the prior art process:

PROCEDURE A (Barrow¹):



PROCEDURE B (new process):



¹reference supra.

Table 1 illustrates the yield advantage provided by the new process.

Table 1. Deprotection of Allyl Ester 11a.

Procedure	mol % Pd(PPh ₃)	Amount of 11a (g)	Yield of 12a (%)	mol % Ph ₃ P/Ph ₃ P=O in 12a (NMR)
A	10	11	32	not detected
A	10	5	58	"
A	10	37	34	"
B	2	1.2	81	3
B	0.2	5	91	not detected
B	0.2	24	94	"

5

The product of process A was contaminated with triphenylphosphine and triphenylphosphine oxide. These contaminants could be partially removed by eluting the crude product through silica gel with organic solvents. However, the acid adheres very strongly to silica gel, and this procedure was impractical for preparing large amounts of 12a.

In the new process, the amount of Pd(PPh₃)₄

catalyst was reduced from 10 to 0.2 mole percent (50 fold reduction), and compound 12a was obtained in greater than 90% yield. Equally important, triphenylphosphine residues in the product were non-detectable by NMR spectroscopy.

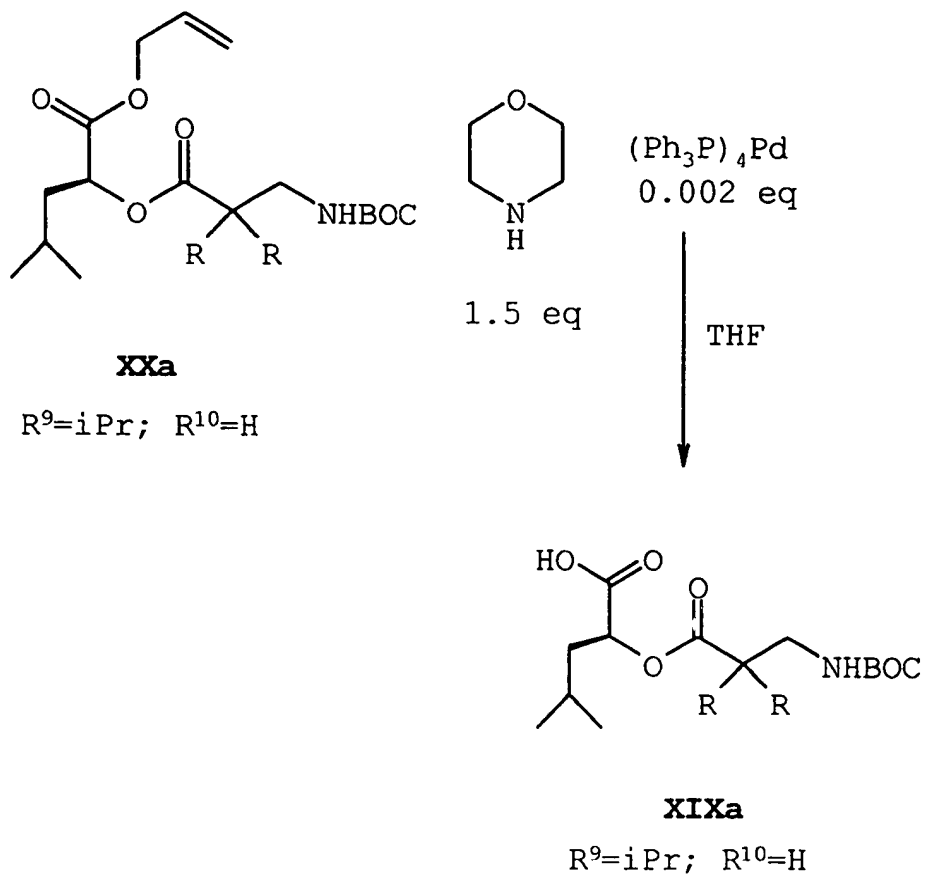
5 Surprisingly, the reaction was complete in less than one hour, even with the lower amounts of catalyst. Thus, Procedure B is simpler, more economical, and provides product with acceptable purity in 90+% yields.

The process of Equation 7 can be run at a
10 temperature of from about zero (0) to about seventy (70) degrees C. A preferred temperature is about 25°C.

Table 2 summarizes the preparation of a number of Formula XIX compounds using this process:

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TABLE 2: Preparation of Formula XIX Compounds by Allyl Ester Deprotection



<u>R</u>	<u>% Yield</u>
19b methyl	91
19c ethyl	99
19d spirocyclopentyl	95
19e spirocyclohexyl	99
19f benzyl	93
19g n-propyl	63
19h i-butyl	34

-25-

Some preferred embodiments are set forth in the following tabular form wherein the features may be independently selected to provide preferred embodiments of this invention. The invention is in no way limited to the
5 features described below:

A) an intermediate of Formula XII wherein R⁶ is halomethoxybenzyl;

B) a compound of Formula XII wherein X' is HCl;

10 C) a process wherein R⁶⁰ in intermediate XV is TBS;

D) a process wherein Ar in intermediate XV is phenyl;
and

E) a process wherein R⁴ and R⁵ in product I, together form a double bond.

15 Appropriate starting materials and reagents to prepare the desired substrates and reagents for the intermediates and processes can be obtained using the guidance of the previous schemes and following examples. Most of the reagents are commercially available, and those
20 which are not can be prepared using accepted chemical methods.

The necessary reaction time is related to the starting materials and operating temperature. The optimum reaction time for a given process is, as always, a compromise which
25 is determined by considering the competing goals of throughput, which is favored by short reaction times, and

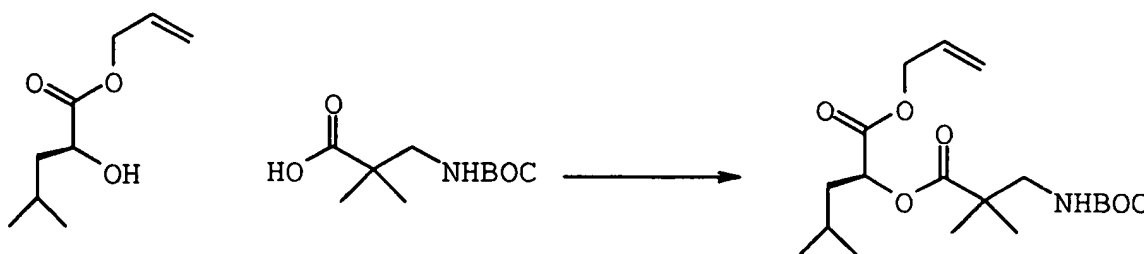
maximum yield, which is favored by long reaction times.

To further illustrate the intermediates and processes of this invention, the following non-limiting examples are provided.

5

Example 1

a) Allyl (2S)-2-[[3-[*tert*-Butoxycarbonyl)amino]-2'-dimethylpropanoyl]oxy]-4-methylpentanoate (**11a**).



10

Fragment D

13

11a

15

20

25

To a solution of 1,1'-carbonyldiimidazole ("CDI", 1346 g, 8.30 mol) in 3 L of THF was added a solution of compound **13** (1803 g, 8.3 mol) in 4 L of THF over 30 min. The reaction was stirred for 2 h at which time NMR analysis showed complete reaction of compound **13**. Fragment D (1450 g, 7.54 mol) was added as a solid, and the reaction mixture was heated to approximately 70 °C for 16 h. The reaction mixture was cooled to 25 °C and concentrated *in vacuo* to give a suspension. Heptane (4 L) was added, and the mixture was extracted with 0.2 N HCl solution (6 L) to remove imidazole. The aqueous layer was extracted with 2 L of heptane. The combined organic layers were extracted successively with 0.2 N HCl solution (3 L), deionized water (3 L), and brine (3 L). The organic layer was dried (sodium sulfate) and concentrated *in vacuo* to give 2984 g of

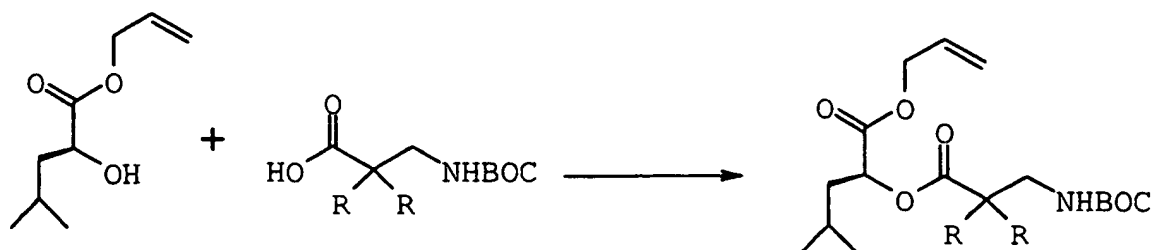
-27-

compound **11a** as an oil. ^1H NMR (CDCl_3 , 500 MHz) δ 0.94 (d, 3H, $J = 8.4$ Hz), 0.98 (d, 3H, $J = 8.4$ Hz), 1.27 (d, 6H, $J = 5$ Hz), 1.45 (s, 9H), 1.71 (m, 3H), 3.31 (m, 2H), 4.66 (m, 2H), 5.1 (m, 1H), 5.3 (m, 3H), 5.9 (m, 1H). ^{13}C NMR (CDCl_3 , 75 MHz) δ 176.4, 170.7, 156.4, 131.5, 119.1, 78.9, 70.9, 66.0, 48.7, 44.0, 39.6, 28.4, 24.9, 23.1, 23.0, 22.3, 21.6. IR (CHCl_3) 3398, 2964, 1739, 1720, 1511, 1472, 1366, 1266, 1252 cm^{-1} . MS {FD $^+$ } m/z (relative intensity) 371 (100).

10 b) **Preparation of 12a**

To a solution of the **11a**, obtained supra, in 8 L of THF was added $\text{Pd}(\text{PPh}_3)_4$ (3.0 g, 2.6 mmol). Morpholine (800 mL, 9.15 mol) was then added dropwise over 30 min at 15-25 $^\circ\text{C}$, and the reaction was then stirred at that temperature for 1.5 h.

15 The reaction mixture was concentrated *in vacuo* to an oil, which was dissolved in 6 L of heptane. The heptane solution was extracted with 1 N HCl (9.8 L). The aqueous layer was back-extracted with 2 L of heptane. The combined organic layers were washed with 3 L of brine, dried (sodium sulfate), and filtered. The filtrate was stirred at room temperature and seeded with 200 mg of compound **12a**. The product crystallized, and the slurry was stirred for 64 h (4 h is sufficient). The slurry was cooled to 0-10 $^\circ\text{C}$ for 3.5 h and filtered. The filter cake was washed with cold
25 heptane (2 x 500 mL) and vacuum dried at 45-50 $^\circ\text{C}$ to give 2324 g (93% overall yield from Fragment D) of compound **12a** as a white solid, mp 70-73 $^\circ\text{C}$.

TABLE 3: Preparation of Formula XX Intermediates

<u>R</u>	<u>Conditions</u>	<u>% Yield</u>
methyl	CDI, 0.1N THF, 17h reflux	94
ethyl	CDI, 1N THF, 72h reflux	78
spirocyclopentyl	CDI, 0.1N THF, 17h reflux	55
spirocyclohexyl	CDI, 0.1N THF, 17h reflux	19
benzyl	CDI, 0.1N THF, 17h reflux	21
n-propyl	CDI, 0.1N THF, 17h reflux	0
n-propyl	CDI, 0.4N PhMe, 17h reflux	59*
i-butyl	CDI, 0.4N PhMe, 17h reflux	52*

* About 50%/wt unknown impurities

5 Example 2 (See Eq. 1)

Preparation of 3-(3-Chloro-4-methoxyphenyl)-D-alanine 2,2,2-trichloroethyl ester hydrochloride salt (1). To a 1000-mL 3-necked flask fitted with a calcium chloride drying tube and a mechanical stirrer and containing a solution of 2 (46.2 g, 100 mmol) in 370 mL of ethyl acetate was added a solution of hydrochloric acid in ethyl acetate (ca. 4.5 M, 800 mmol). After stirring for 19 h at room temperature, the

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resulting thick white reaction was cooled to 0 °C and filtered. The collected solid was washed with cold ethyl acetate (1 x 90 mL) followed by drying *in vacuo* at 40 °C to provide 36.9 g (93%) of compound 1 as a white powder: mp 5 217-219 °C; $[\alpha] +3.1^\circ$ (c 1.21, MeOH); IR (KBr) 2830 (m), 1755 (s), 1502 (s), 1282 (s), 1258 (s), 1229 (s), 814 (s) cm^{-1} ; 500 MHz ^1H NMR ($\text{DMSO}-d_6$) δ 8.88 (br s, 3H), 7.45 (d, 1H, $J = 2.0$ Hz), 7.28 (dd, 1H, $J = 8.5, 2.0$ Hz), 7.11 (d, 1H, $J = 8.5$ Hz), 5.01 and 4.96 (AB quartet, 2H, $J = 12.2$ Hz), 4.48 10 (t, 1H, $J = 6.6$ Hz), 3.84 (s, 3H), 3.23 (dd, 1H, $J = 14.4, 5.9$ Hz), 3.17 (dd, 1H, $J = 14.4, 7.3$ Hz); 125 MHz ^{13}C NMR ($\text{DMSO}-d_6$) δ 168.8, 154.7, 131.8, 130.3, 128.4, 121.9, 113.8, 95.2, 75.1, 57.0, 53.8, 35.3. Anal. calcd. for $\text{C}_{12}\text{H}_{14}\text{Cl}_5\text{NO}_3$: C, 36.26; H, 3.55; N, 3.52. Found: C, 36.24; H, 3.59; N, 15 3.44.

Example 3 (See Eq. 2)

Preparation of Ene-amide 4. A solution of acid 3 (551 mg, 1.53 mmol) in 3.1 mL of DMF was treated with N,N- 20 diisopropylethylamine (799 mL, 4.58 mmol). Upon cooling to 0 °C, the mixture was treated with diphenylphosphinic chloride (306 mL, 1.60 mmol). After the reaction was stirred at 0 °C for 5 min and at room temperature for 30 min, hydrochloride salt 1 (668 mg as a solid, 1.68 mmol) was 25 added over ca. 3 min. The mixture was allowed to stir for 1 h 15 min at which time the reaction was poured onto 20 mL of

-30-

water and washed with diethyl ether (2 x 20 mL). The combined organic extracts were washed with 1N hydrochloric acid (1 x 10 mL). The acid wash was extracted with diethyl ether (1 x 10 mL); and the combined organic extracts were
5 dried (MgSO_4), filtered, and concentrated *in vacuo* to a yellow oil. Chromatography on 55 g of flash silica gel, eluting with ethyl acetate:hexanes (1:4), afforded 903 mg (84%) of compound 4 as a faint yellow foam.

Example 4 (see Eq. 4)

10 **Preparation of Cryptophycin 51 (compound 6).**

To a solution of cryptophycin seco-acid 5 (671 mg, 0.963 mmol) in 10 mL of DMF was added N,N-diisopropylethylamine (503 mL, 2.89 mmol), followed by diphenylphosphinic chloride (202 mL, 1.06 mmol). After being stirred at room
15 temperature for 3 h, the reaction was diluted with ethyl acetate (50 mL) and washed successively with water (1 x 25 mL), 1 N HCl (1 x 25 mL), saturated aqueous NaHCO_3 (1 x 25 mL), and brine (1 x 25 mL). Each aqueous layer was washed with ethyl acetate (1 x 25 mL). The combined organic
20 extracts were dried (Na_2SO_4), filtered, and concentrated *in vacuo* to a crude solid residue which was diluted with ethyl acetate. After standing at room temperature overnight, the mixture was filtered to provide 188 mg (30%) of 6 as a white solid. The filtrate was chromatographed over flash silica
25 gel, eluting with ethyl acetate:hexanes (2:1 followed by 3:1) to afford another 304 mg (48%) of compound 6.

Example 5 (See Eq. 6)**a) Preparation of Ethyl 2-cyano-2-methylpropanoate (8a).**

Cesium carbonate (4324 g, 13.27 mol) and DMF (2.25 L) were
5 added to a 22 L flask with an overhead stirrer. Methyl
iodide (2828 g, 19.9 mol), was added and the mixture was
cooled to -10 °C under nitrogen. Ethyl cyanoacetate (750 g,
6.63 mol) was added over 30 min, keeping the reaction
temperature below 30 °C. The cooling bath was removed, and
10 the reaction mixture was stirred for 2 h. The reaction
mixture was then filtered, and the salt cake was washed with
6 L of methyl tert-butylether (MTBE). The filtrate was
combined with 3 L of 0.1N HCl and the layers were separated.
The aqueous layer was extracted with 3 L of MTBE. The
15 combined organic layers were washed with 5% LiCl solution (2
x 3 L), dried with sodium sulfate, and concentrated via
distillation at atmospheric pressure to give compound 8a as
a light yellow oil. The oil was vacuum distilled at 50-60
°C, 10 mm Hg to give 882 g (94% yield) of 2 as a colorless
20 oil. ¹H NMR (CDCl₃, 500 MHz) δ 1.32 (t, 3H), 1.60 (s, 6H),
4.26 (m, 2H). ¹³C NMR (CDCl₃, 75 MHz) δ 169.8, 120.9, 62.9,
38.7, 31.7, 24.9, 14.1. IR (CHCl₃) 3021, 2994, 2944, 2909,
2877, 2247, 1743, 1469, 1388, 1369, 1266, 1156 cm⁻¹. MS
{FD⁺} m/z (relative intensity): 142.1 (100). Anal. Calcd
25 for C₇H₁₁NO₂: C, 59.56; H, 7.85; N, 9.92. Found: C, 58.90;

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H, 7.39; N, 10.00.

b) Preparation of Ethyl 3-[(*tert*-butoxycarbonyl)amino]-2,2-dimethylpropanoate (9a).

5 To a 500 mL stainless steel autoclave were charged 5% rhodium on alumina (2.5 g), BOC anhydride (8.4 g, 38.5 mmol), compound 8a (5.0 g, 35.4 mmol) and THF (140 mL). The stirred mixture was placed under 60 psi hydrogen at 70 °C. After 16 h, an NMR spectrum of the reaction mixture showed
10 the reaction was complete. The reaction mixture was allowed to cool to 25 °C, vented, and purged with nitrogen. The mixture was then filtered through a Celite pad and concentrated *in vacuo* to give 8.64 g (99% crude yield) of compound 9a as an oil. ¹H NMR (CDCl₃, 500 MHz) δ 1.06 (s, 6H), 1.15 (t, 3H), 1.32 (s, 9H), 3.1 (d, 2H), 4.05 (m, 2H),
15 5.0 (bs, 1H). ¹³C NMR (CDCl₃, 300 MHz) δ 177.3, 156.3, 79.2, 60.8, 48.4, 43.7, 28.5, 23.1, 14.3. IR (CHCl₃) 3691, 3457, 2983, 2936, 2875, 1714, 1602, 1509, 1473, 1367, 1312, 1240, 1155 cm⁻¹. MS {FD⁺} m/z (relative intensity) 245.2 (100).
20 Anal. Calcd. for C₁₂H₂₃NO₄: C, 58.75; H, 9.45; N, 5.71. Found: C, 58.40; H, 8.95; N, 5.65.

c) Compound 10

To Compound 9a (164.2 g, approximately 670 mmol) was added
25 1.4 L of 5N NaOH, and the mixture was stirred under a

-33-

nitrogen atmosphere until homogeneous (48 h). CH_2Cl_2 (1.3 L) was added, and the mixture was cooled to 10 °C. The pH of the aqueous layer was adjusted to 3 by adding (dropwise) 1L of 6N HCl followed by 400 mL of 1N HCl. The temperature was maintained below 20 °C. The mixture stirred for 20 min, and the layers were separated. The aqueous layer was extracted with 1 L of CH_2Cl_2 . The organic layers were combined, dried over Na_2SO_4 and concentrated *in vacuo* to give 116.8 g of a crude yellow solid. The solid was stirred in 400 mL of hexane for 4 h. The slurry was filtered and the solid dried to give 114.7 g (78% yield) of compound 10 as a white solid, mp 115-16 °C. ^1H NMR (CDCl_3 , 500 MHz) δ 1.23 (s, 6H), 1.48 (s, 9H), 3.26 (bs, 2H), 5.09 (bs, 0.7 H), 6.41 (bs, 0.3 H), 11.68 (bs, 1H). ^{13}C NMR (CDCl_3 , 75 MHz) δ 183.3, 181.7, 158.5, 156.4, 81.6, 79.6, 49.7, 48.1, 44.1, 43.7, 28.5, 23.0. IR (CHCl_3) 3315, 3004, 2542, 1895, 1700, 1648, 1414, 1367, 1350, 1278, 1157. MS {FD $^+$ } m/z (relative intensity) 173 (19), 218 (100). Anal. Calcd for $\text{C}_{10}\text{H}_{19}\text{NO}_4$: C, 55.28; H, 8.81; N, 6.45. Found: C, 55.33; H, 8.59; N, 6.33.

Example 6 (See Eq. 6)**Large Scale Preparation.**a) Compound 9a

To a 10 gallon stainless steel autoclave were
5 charged 5% rhodium on alumina (390 g), BOC anhydride (1363
g, 6.25 mol), compound 8a (prepared as described by Example
4) (779 g, 5.52 mol), and THF (20 L). The stirred mixture
was placed under 60 psi hydrogen at 70 °C. After 22 h, an
NMR spectrum of the reaction mixture showed 83% conversion
10 to 9a. Additional 5% rhodium on alumina catalyst (195 g)
was added. The hydrogenation was continued for another 4 h,
at which time NMR assay of the reaction mixture showed 98%
conversion. The reaction mixture was allowed to cool to 25
°C, vented, and purged with nitrogen. The mixture was then
15 filtered through a multi-plate filter and concentrated *in*
vacuo to give 1173 g (87% yield) of compound 9a as an oil,
which was used directly in the next step.

b) Preparation of 3-[(*tert*-Butoxycarbonyl)amino]-2,2-
dimethylpropanoic acid (10).

20

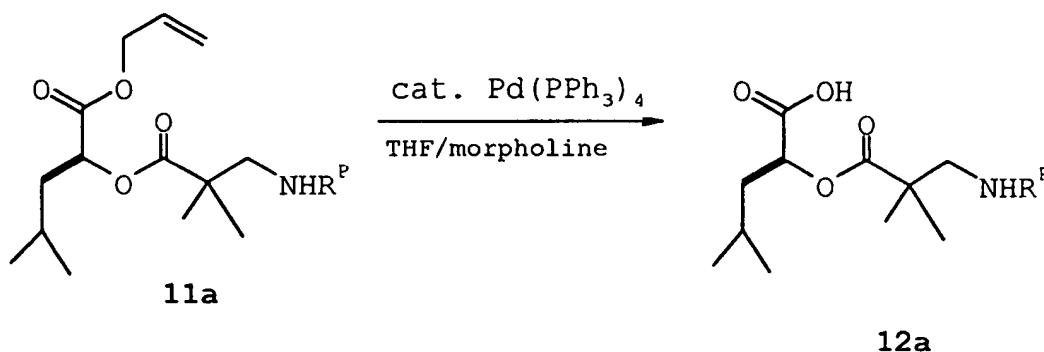
Two 22 L flasks were each charged with compound 9a (583 g,
2.38 mol), LiOH·H₂O (204.5 g, 4.87 mol), THF (5.7 L), and
water (4.75 L). The reaction mixtures were heated to 64 °C
for 19 h. The mixtures were then cooled to 10 °C with an
25 ice bath. Approximately 1 L of 6N HCl was added to each

-35-

reaction mixture to bring the pH to 3-3.5. Each mixture was combined with 2.9 L of CH₂Cl₂, and the aqueous layers were separated. The aqueous layers were extracted with another 1.5 L portion of CH₂Cl₂. The combined organic layers were
5 dried with sodium sulfate and concentrated *in vacuo* to give a white solid. The solid was slurried in 5 L of heptane for 1 h, filtered, and vacuum dried to give 830 g (80% yield) of compound 10 as a white solid, mp 114-116 °C. Anal. Calcd for C₁₀H₁₉NO₄: C, 55.28; H, 8.81; N, 6.45. Found: C, 55.55;
10 H, 8.77; N, 6.56.

Example 7

(2*S*)-2-[[[3'-[(*tert*-Butoxycarbonyl)amino]-2',2'-dimethylpropanoyl]oxy]-4-methylpentanoic Acid (12a).

(R^P=BOC)

A three-neck flask with an overhead stirrer was charged with compound 11a (23.92 g, 64.5 mmol), Pd(PPh₃)₄ (149 mg, 0.13 mmol), and dry THF (100 mL). The mixture was cooled to 8 °C
20 under nitrogen. Morpholine (6.8 mL, 77.4 mmol) in 10 mL of THF was add dropwise over 10 min. No exotherm was observed.

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The cooling bath was removed, and the solution was stirred for 1 h. The solvent was then removed from the reaction mixture under vacuum. The resulting viscous oil was dissolved in 250 mL of hexane, and 70 mL of 0.01N HCl was added. Then, 1N HCl (77 mL) was added dropwise over 5 min.

A small amount of yellow precipitate formed at the interface. The layers were separated, and the aqueous layer was extracted with 100 mL of hexane. The combined hexane layers were filtered to remove residual palladium complexes, dried with sodium sulfate, and concentrated *in vacuo* to obtain 21.3 g of **12a** as a very viscous oil. (The NMR spectrum showed 6% (by weight) hexane in the oil; corrected yield of **12a** = 94%.) $[\alpha]_D = -34.2^\circ$ (c 0.032, CHCl₃). ¹H NMR (CDCl₃, 500 MHz) δ 0.97 (d, J = 6.3, 3H), 0.99 (d, J = 6.3 Hz, 3H), 1.22 (d, J = 9.0 Hz, 6H), 1.43 (s, 9H), 1.75 (m, 3H), 3.31 (m, 2H), 5.09 (dd, J = 9.7, 3.4 Hz, 1H), 5.5 (bs, 0.7H), 6.16 (bs, 0.3H), 10.5 (bs, 1H). ¹³C NMR (CDCl₃, 75 MHz) δ 176.6, 175.6, 156.8, 79.4, 70.6, 48.6, 44.0, 39.6, 28.4, 24.9, 23.1, 22.2, 21.5. IR (CHCl₃) 3691, 2963, 1710, 1512, 1151 cm⁻¹. MS (FD⁺) m/z (relative intensity) 332 (100). Anal. Calcd. for C₁₆H₂₉NO₆: C, 57.99; H, 8.82; N, 4.23. Found: C, 58.05; H, 8.72; N, 4.13.

Example 8

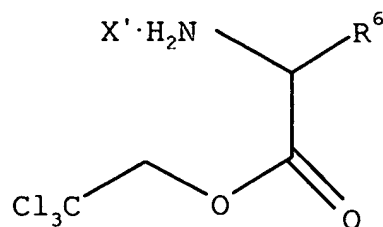
Preparation of [5S-(2E,5R*,6S*,7E)]-3-chloro-N-[5-[[[(1,1-dimethylethyl)dimethylsilyl]oxy]-6-methyl-1-oxo-8-phenyl-2,7-octadienyl]-O-methyl-2,2,2-trichloroethyl ester D-

5 Tyrosine (4).

A solution of acid 3 (130 mg, 0.361 mmol) in 720 μ L of DMF was treated with N,N-diisopropylethylamine (188 μ L 1.08 mmol), followed by diphenyl chlorophosphate (82 μ L , 0.396 mmol). After the mixture had stirred for 1 h, hydrochloride salt 1 (157 mg, 0.395 mmol) was added as a solid. The mixture was allowed to stir for 2 h 45 min at which time the reaction was diluted with diethyl ether (15 ml) and washed with 1N hydrochloric acid (10 mL), saturated sodium bicarbonate solution (10 mL), and brine (10 mL). The organic phase was dried (MgSO_4), filtered, and concentrated *in vacuo* to a yellow oil. Chromatography on 15 g of flash silica gel, eluting with ethyl acetate:hexanes (1:2), afforded 199 mg (78%) of compound 4 as a faint yellow oil.

Claims

1. A compound of Formula XII

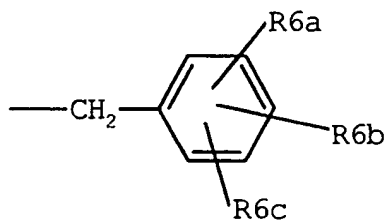


XII

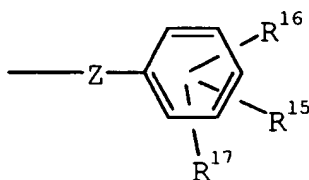
wherein X' represents a strong acid; and

R^6 is C_1 - C_6 alkyl, substituted (C_1 - C_6)alkyl, (C_3 - C_8)cycloalkyl, substituted C_3 - C_8 cycloalkyl, a heteroaromatic or substituted heteroaromatic group, or a group of formula

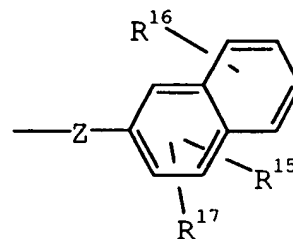
10 IIIa, III' or III'':



IIIa



III'



III''

wherein

R^{6a} , R^{6b} , and R^{6c} independently are H, halo or OR^{18} ;

15 R^{15} , R^{16} , and R^{17} independently are hydrogen, halo, (C_1 - C_6)alkyl, OR^{18} , O-aryl, NH_2 , $\text{NR}^{18}\text{R}^{19}$, NO_2 , $\text{OP}(\text{O})_2\text{H}_2$, (C_1 - C_6 alkoxy)phenyl, Sbenzyl, CONH_2 , CO_2H , PO_3H_2 , SO_2R^{23} , or Z' ;

R^{18} and R^{19} independently are hydrogen or C_1 - C_6 alkyl;

R^{23} is hydrogen or (C_1 - C_3)alkyl;

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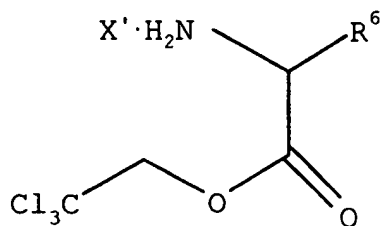
Z is $-(CH_2)_n-$ or (C_3-C_5) cycloalkyl;

n is 0, 1, or 2; and

Z' is an aromatic or substituted aromatic group.

- 5 2. A compound of **Claim 1** wherein R^6 is halomethoxybenzyl.

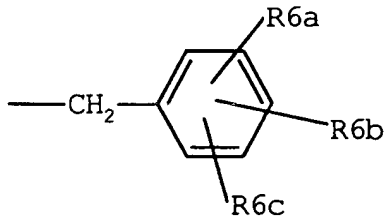
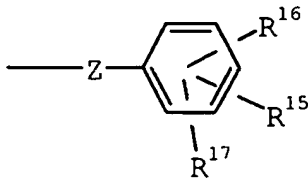
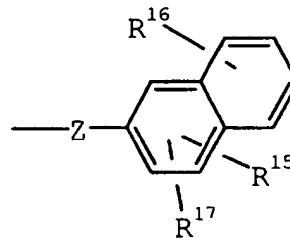
3. A process for preparing a compound of Formula **XII**

**XII**

wherein **X'** represents a strong acid; and

R^6 is C_1-C_6 alkyl, substituted (C_1-C_6) alkyl, (C_3-C_8) cycloalkyl, substituted C_3-C_8 cycloalkyl, a heteroaromatic or substituted heteroaromatic group, or a group of formula

15 **IIIa**, **III'** or **III''**:

**IIIa****III'****III''**

wherein

R^{6a} , R^{6b} , and R^{6c} independently are H, halo or OR^{18} ;

20 R^{15} , R^{16} , and R^{17} independently are hydrogen, halo, $(C_1-$

-40-

C₆)alkyl, OR¹⁸, O-aryl, NH₂, NR¹⁸R¹⁹, NO₂, OP0₄H₂, (C₁-C₆ alkoxy)phenyl, Sbenzyl, CONH₂, CO₂H, PO₃H₂, SO₂R²³, or Z';

R¹⁸ and R¹⁹ independently are hydrogen or C₁-C₆ alkyl;

R²³ is hydrogen or (C₁-C₃)alkyl;

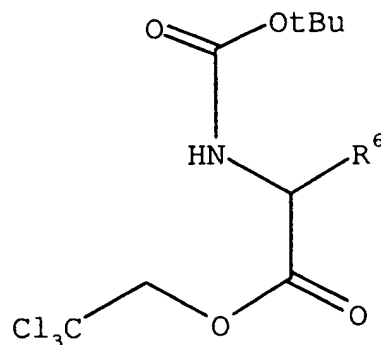
5 Z is -(CH₂)_n- or (C₃-C₅)cycloalkyl;

n is 0, 1, or 2; and

Z' is an aromatic or substituted aromatic group;

comprising

contacting a compound of formula XII'



XII'

10

with a strong acid.

4. A process of Claim 3 wherein R⁶ is halomethoxybenzyl.

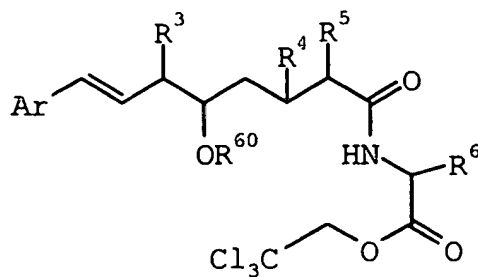
15

5. A process of Claim 3 wherein the acid is hydrochloric acid.

6. A process for preparing a compound of Formula

20 XIII

-41-



XIII

wherein

Ar is an aromatic or heteroaromatic group, or a substituted

5 aromatic or heteroaromatic group;

R⁶⁰ is an alcohol protecting group;

R³ is C₁-C₆ alkyl;

R⁴ and **R⁵** are H; or

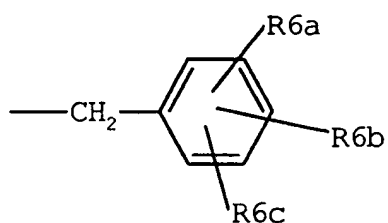
R⁴ and **R⁵** together form a second bond;

10 **R⁶** is C₁-C₆alkyl, substituted (C₁-C₆)alkyl, (C₃-C₈)cycloalkyl,

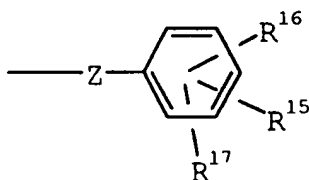
substituted C₃-C₈ cycloalkyl, a heteroaromatic or

substituted heteroaromatic group, or a group of formula

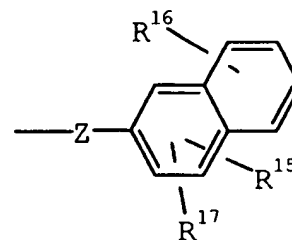
IIIa, III' or III'':



IIIa



III'



III''

15

wherein

R^{6a}, **R^{6b}**, and **R^{6c}** independently are H, halo or OR¹⁸;

-42-

R^{15} , R^{16} , and R^{17} independently are hydrogen, halo, (C_1-C_6) alkyl, OR^{18} , O-aryl, NH_2 , $NR^{18}R^{19}$, NO_2 , $OP(=O)(OH)_2$, (C_1-C_6) alkoxy)phenyl, Sbenzyl, $CONH_2$, CO_2H , PO_3H_2 , SO_2R^{23} , or Z' ;

R^{18} and R^{19} independently are hydrogen or C_1-C_6 alkyl;

5 R^{23} is hydrogen or (C_1-C_3) alkyl;

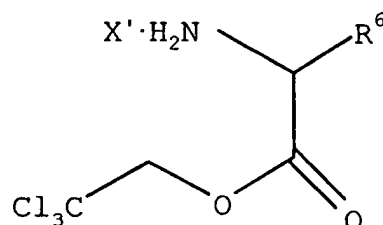
Z is $-(CH_2)_n-$ or (C_3-C_5) cycloalkyl;

n is 0, 1 or 2; and

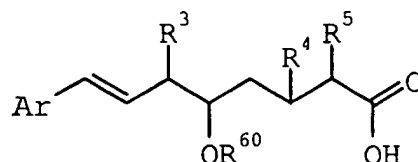
Z' is an aromatic or substituted aromatic group;

comprising

10 contacting 1) a compound of the Formula XII



wherein X' represents a strong acid; with 2) a compound of the Formula XV



XV

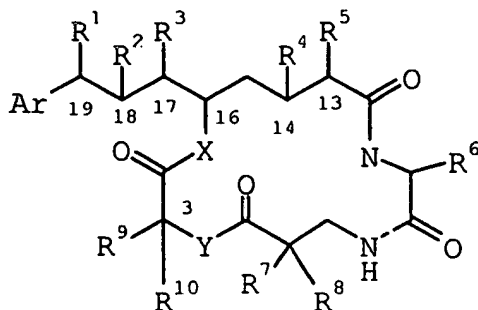
15 3) an $(R^A)_2$ phosphinic halide, wherein R^A is C_1-C_6 alkyl, C_1-C_6 aralkyl or Ar; and 4) a base.

7. A process of Claim 6 wherein X' is HCl.

8. A process of Claim 6 wherein R^{60} is TBS.

9. A process of Claim 7 wherein the base is N,N-diisopropylethylamine.

10. A process for preparing a compound of Formula I



I

wherein

Ar is an aromatic or heteroaromatic group, or a substituted aromatic or heteroaromatic group;

R¹ is halo, SR, OR, amino, mono or di-(C₁-C₆-alkyl)amino,

10 tri(C₁-C₆-alkyl)ammonium, C₁-C₆-alkylthio, di(C₁-C₆-alkyl)sulfonium, C₁-C₆-alkylsulfonyl, or C₁-C₆-alkylphosphonyl; and

R² is OH or SH; or

15 R¹ and R² taken together form a second bond between C-18 and C-19 or together form an epoxide, aziridine, episulfide, or cyclopropyl ring;

R is H, C₁-C₆ alkyl, C₁-C₆ alkanoyl or Ar;

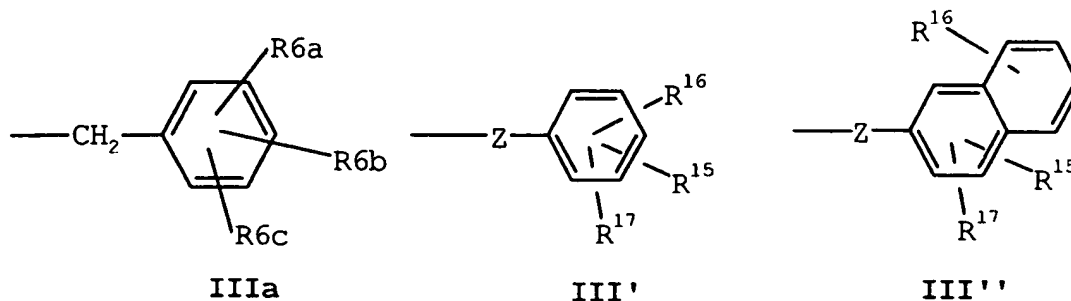
R³ is C₁-C₆ alkyl;

R⁴ and R⁵ are H; or

20 R⁴ and R⁵ together form a second bond;

R⁶ is C₁-C₆alkyl, substituted (C₁-C₆)alkyl, (C₃-C₈)cycloalkyl, substituted C₃-C₈ cycloalkyl, a heteroaromatic or substituted heteroaromatic group, or a group of formula

IIIa, III' or III'':



wherein

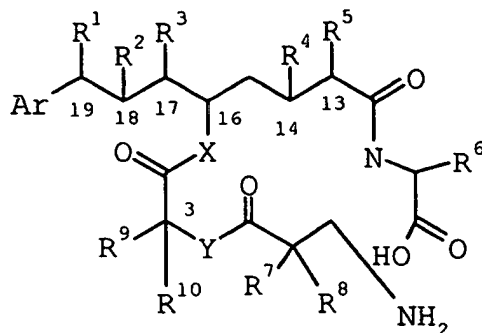
- 5 R^{6a} , R^{6b} , and R^{6c} independently are H, halo or OR^{18} ;
 R^7 is H, $\text{C}_1\text{--C}_6$ alkyl, $\text{C}_2\text{--C}_6$ -alkenyl, $\text{C}_2\text{--C}_6$ -alkynyl, benzyl, or benzyl substituted with up to three substituents independently selected from $\text{C}_1\text{--C}_6$ -alkyl, halo, $\text{C}_1\text{--C}_6$ -alkoxy, amino or $\text{NR}^{51}\text{R}^{52}$; and
- 10 R^8 is H or $\text{C}_1\text{--C}_6$ alkyl; or
 R^7 and R^8 together form a $\text{C}_3\text{--C}_8$ cycloalkyl ring;
 R^{51} and R^{52} independently are $\text{C}_1\text{--C}_3$ alkyl;
 R^9 is H, $\text{C}_1\text{--C}_6$ alkyl, $\text{C}_2\text{--C}_6$ alkenyl, $\text{C}_2\text{--C}_6$ -alkynyl or $(\text{C}_1\text{--C}_6 \text{ alkyl})\text{C}_3\text{--C}_5$ cycloalkyl;
- 15 R^{10} is H or $\text{C}_1\text{--C}_6$ alkyl;
 X is O, NH or $(\text{C}_1\text{--C}_3 \text{ alkyl})\text{N-}$; and
 Y is C, O, NH, S, SO, SO_2 or $(\text{C}_1\text{--C}_3 \text{ alkyl})\text{N-}$;

comprising

contacting

- 20 1) a compound of Formula XVI

-45-



XVI

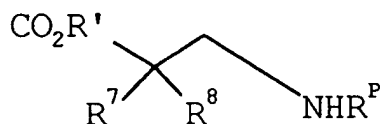
with 2) an $(R^A)_2$ phosphinic halide, wherein R^A is C_1 - C_6 alkyl;
and 3) a base.

5

11. A process of Claim 10 wherein the base is N,N-diisopropylethylamine.

12. A process of Claim 11 wherein R^6 is
10 halomethoxybenzyl.

13. A process for preparing a compound of Formula XVII



XVII

15

wherein R' is hydrogen or C_1 - C_6 alkyl;
 R^7 is H, C_1 - C_6 alkyl, C_2 - C_6 -alkenyl, C_2 - C_6 -alkynyl, benzyl, or
benzyl substituted with up to three substituents
independently selected from C_1 - C_6 -alkyl, halo, C_1 - C_6 -alkoxy,
20 amino or $NR^{51}R^{52}$; and

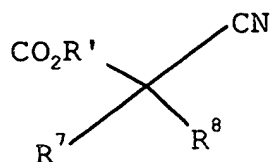
R^8 is H or C_1 - C_6 alkyl; or

R^7 and R^8 together form a C_3 - C_8 cycloalkyl ring; and

R^P is *tert*-butoxycarbonyl or benzyloxycarbonyl;

comprising contacting a compound of the Formula XVIII

-46-



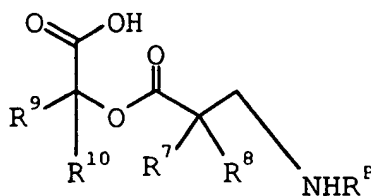
XVIII

with a rhodium catalyst.

5

14. A process of **Claim 13** wherein the rhodium catalyst is rhodium on alumina.

15. A process for preparing a compound of Formula **XIX**



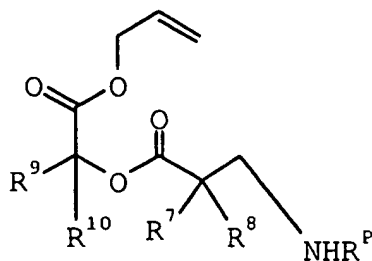
XIX

10

wherein

R^7 , R^8 , R^9 and R^{10} independently are H or C_1 - C_6 alkyl; and R^P is *tert*-butoxycarbonyl or benzyloxycarbonyl;

15 comprising contacting a compound of Formula **XX**



XX

20 in the presence of 1) a catalytic quantity of less than about four (4) mole percent of $Pd(PPh_3)_4$ and 2) an allyl scavenger.

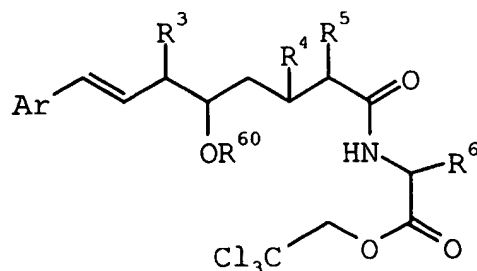
-47-

16. A process of Claim 15 wherein the catalytic quantity is less than about two (2) mole percent.

17. A process of Claim 16 wherein the catalytic
5 quantity is about two tenths mole percent (0.2%).

18. A process of Claim 16 wherein the allyl scavenger is morpholine.

10 19. In the process for preparing a compound of formula XIII



XIII

wherein

15 **Ar** is an aromatic or heteroaromatic group, or a substituted aromatic or heteroaromatic group;

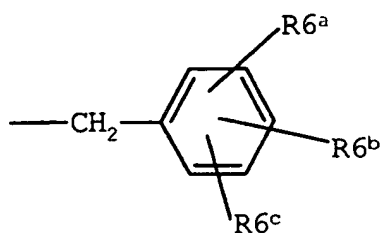
R⁶⁰ is an alcohol protecting group;

R³ is C₁-C₆ alkyl;

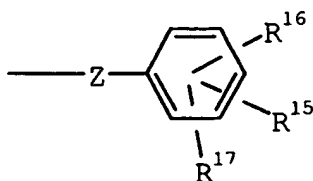
R⁴ and **R⁵** are H; or

20 **R⁴** and **R⁵** together form a second bond;

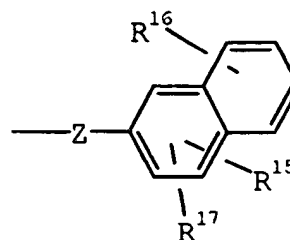
R⁶ is C₁-C₆alkyl, substituted (C₁-C₆)alkyl, (C₃-C₈)cycloalkyl, substituted C₃-C₈ cycloalkyl, a heteroaromatic or substituted heteroaromatic group, or a group of formula IIIa, III' or III":



IIIa



III'



III''

wherein

R^{6a} , R^{6b} , and R^{6c} independently are H, halo or OR^{18} ;

5 R^{15} , R^{16} , and R^{17} independently are hydrogen, halo, (C_1-C_6) alkyl, OR^{18} , O-aryl, NH_2 , $NR^{18}R^{19}$, NO_2 , $OP(O)_2H$, $(C_1-C_6$ alkoxy)phenyl, Sbenzyl, $CONH_2$, CO_2H , PO_3H_2 , SO_2R^{23} , or Z' ;

R^{18} and R^{19} independently are hydrogen or C_1-C_6 alkyl;

R^{23} is hydrogen or (C_1-C_3) alkyl;

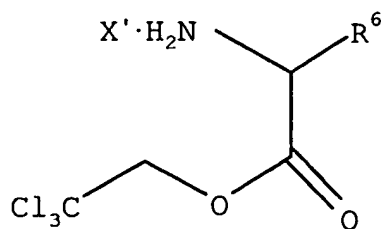
10 Z is $-(CH_2)_n-$ or (C_3-C_5) cycloalkyl;

n is 0, 1 or 2; and

Z' is an aromatic or substituted aromatic group;

comprising

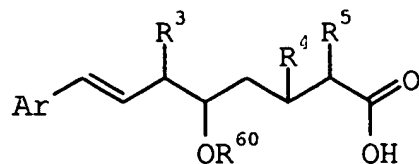
by reacting 1) a compound of formula XII



XII

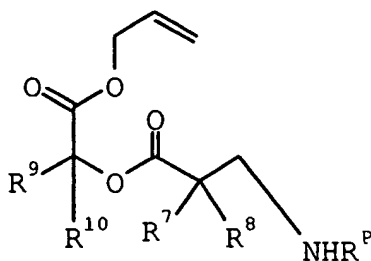
15 wherein X' represents a strong acid; and 2) a compound of formula XV

-49-

**XV**

2) with a coupling reagent and 3) an amine, the improvement
 which comprises using diphenyl chlorophosphate as the
 5 coupling agent.

20. In the process for preparing a compound
 of formula **XX**

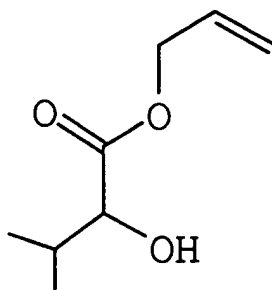
**XX**

- 10 wherein R^7 is H, C_1 - C_6 alkyl, C_1 - C_6 -alkenyl, C_2 - C_6 -alkynyl,
 benzyl, or benzyl substituted with up to three substituents
 independently selected from C_1 - C_6 -alkyl, halo, C_1 - C_6 -alkoxy,
 amino or $NR^{51}R^{52}$; and
 R^8 is H or C_1 - C_6 alkyl; or
 15 R^7 and R^8 together form a C_3 - C_8 cycloalkyl ring;
 R^9 is H, C_1 - C_6 alkyl, C_2 - C_6 alkenyl, C_2 - C_6 -alkynyl or $(C_1$ - C_6
 alkyl) C_3 - C_5 cycloalkyl;
 R^{10} is H or C_1 - C_6 alkyl; and

-50-

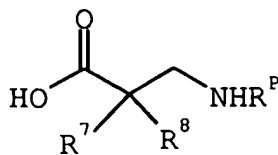
R^p is tert-butoxycarbonyl or benzyloxycarbonyl;

by coupling a Fragment D compound of the formula:



D

5 and a Fragment C compound of the formula:



C

provided that R^7 and R^8 cannot be H; in an inert organic solvent;

10 the improvement comprising using the coupling reagent 1,1'-carbonyldiimidazole.

21. An improvement of Claim 21 wherein R^7 and R^8 are methyl.

15

22. An improvement of Claim 21 wherein R^p is BOC.

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) : Please See Extra Sheet.

US CL : Please See Extra Sheet.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 540/454, 460; 560/38, 39, 41, 58, 121, 122, 123, 124, 125, 155, 171; 562/454, 460

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 3,567,834 A (GRANATEK ET AL.) 02 March 1971 (02/03/71).	1-22
A	WO 95/17093 A1 (UNIVERSITY OF HAWAII) 29 June 1995 (29/06/95).	1-22



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents:	*T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
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O document referring to an oral disclosure, use, exhibition or other means	
P document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search

06 NOVEMBER 1997

Date of mailing of the international search report

15 DEC 1997

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Authorized officer

ROBERT T. BOND aco

Telephone No. (703) 308-1235

A. CLASSIFICATION OF SUBJECT MATTER:

IPC (6):

C07D 291/02, 285/00, 273/00; C07C 229/12, 227/18, 231/02, 235/26, 227/06, 227/16

A. CLASSIFICATION OF SUBJECT MATTER:

US CL :

540/454, 460; 560/38, 39, 41, 58, 121, 122, 123, 124, 125, 155, 171; 562/454, 460

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